

## IT IS CLAIMED:

1. A liposome composition for fusion with a target membrane of a cell, liposome, or the like, comprising  
5 a suspension of liposomes designed for targeting to the target membrane, where each liposome contains a therapeutic agent entrapped in the liposomes, an outer liposome surface having a coating of chemically releasable hydrophilic polymer chains, and  
10 hydrophobic polymers on the liposome outer surface, said polymers being shielded by the hydrophilic polymer coating and exposed for fusion with said target membrane when the hydrophilic polymer coating is chemically released.
- 15 2. The composition of claim 1, wherein said hydrophilic polymer and said hydrophobic polymer form a diblock copolymer in which said hydrophilic polymer and said hydrophobic polymer are joined by a chemically  
20 releasable bond.
3. The composition of claim 2, wherein said releasable bond is a disulfide bond or a pH sensitive chemical linkage.
- 25 4. The composition of claim 1, wherein said hydrophilic polymer coating is composed of a hydrophilic polymer selected from the group consisting of polyvinylpyrrolidone, polyvinylmethylether, polymethyloxazoline, polyethyloxazoline, polyhydroxypropyloxazoline, polyhydroxypropylmethacrylamide, polymethacrylamide, polydimethylacrylamide, polyhydroxypropylmethacrylate, polyhydroxyethylacrylate, hydroxymethylcellulose, hydroxyethylcellulose, polyethyleneglycol, and polyaspartamide.  
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5. The composition of claim 4, wherein said hydrophilic polymer coating is composed of polyethylene glycol chains having a molecular weight of between 500-10,000 daltons.

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6. The composition of claim 1, wherein said hydrophobic polymer is selected from the group consisting of polypropylene oxide, polyethylene, polypropylene, polycarbonate, polystyrene, polysulfone, polyphenylene oxide and polytetramethylene ether.

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7. The composition of claim 6, wherein said hydrophobic polymer is polypropylene oxide having a molecular weight of between 500-3,000 daltons.

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8. The composition of claim 1, wherein said hydrophobic polymer is a linear polymer effective to cause hemolysis of red blood cells when a water-soluble triblock copolymer containing the hydrophobic polymer and hydrophilic polymer chains joined to opposite ends of the hydrophobic polymer chains by disulfide bonds is incubated with such cells, and the incubate is treated with a reducing agent.

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9. The composition of claim 1, wherein said liposomes further contain an unshielded ligand attached to the hydrophilic polymer coating effective for ligand-specific binding to a receptor molecule on a target cell surface prior to chemical release of the hydrophilic polymer coating.

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10. The composition of claim 9, wherein said ligand is selected from the group consisting of (i) folate, where the composition is intended for treating tumor cells having cell-surface folate receptors, (ii)

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pyridoxyl, where the composition is intended for treating virus-infected CD4+ lymphocytes, and (iii) sialyl-Lewis<sup>x</sup>, where the composition is intended for treating a region of inflammation.

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11. The composition of claim 1, wherein the liposomes further include a shielded ligand attached to the liposome effective to bind to a target cell surface receptor molecules after, but not before, chemical release of the hydrophilic polymer coating.

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12. The composition of claim 1, wherein said liposomes further contain a shielded cationic lipid effective to impart a positive liposome-surface charge, to enhance binding of liposomes to target cells after, but not before, chemical release of the hydrophilic polymer coating.

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13. The composition of claim 1, wherein the agent entrapped in the lipid vesicles is a polynucleotide capable of expressing a selected protein, when taken up by a target cell.

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14. The composition of claim 1, wherein the agent entrapped in the liposomes is an oligonucleotide or oligonucleotide analog effective for sequence-specific binding to cellular RNA or DNA.

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15. A method of delivering a compound to target cells in a subject, comprising

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parenterally administering to the subject, liposomes designed for reaching the target cells via the bloodstream, each liposome containing said compound in entrapped form and having an outer surface coating of chemically releasable hydrophilic polymer chains, and

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contacting the liposomes at the target cells with a chemical agent effective to release said chains forming said surface coating, thereby to expose hydrophobic polymers on the liposome outer surface for interaction with outer cell membranes of the target cells and promote fusion of the liposome with the target cells.

16. The method of claim 15, wherein said hydrophilic polymer chains are releasably attached to the liposome via a reducible chemical linkage, and said contacting includes administering to the subject a reducing agent effective to release said chains.

17. The method of claim 16, wherein said chemical linkage is a disulfide linkage and said reducing agent is selected from the group consisting of cysteine, glutathione and ascorbate.

18. The method of claim 15, wherein each of said hydrophilic polymer chains is releasably attached to the liposome via a pH sensitive chemical linkage, and said contacting includes targeting the liposomes to a site having a pH effective to release said chains.

19. The method of claim 18, wherein said liposomes have sizes between 0.03-0.40  $\mu\text{m}$  for extravasation into a solid tumor.

20. The method of claim 15, wherein said liposomes further contain an unshielded ligand attached to the hydrophilic polymer coating effective for ligand-specific binding to a receptor molecule on a target cell surface before chemical release of the hydrophilic polymer coating.

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21. The method of claim 20, wherein said ligand is selected from the group consisting of (i) folate, where the composition is intended for treating tumor cells having cell-surface folate receptors, (ii) pyridoxyl, where the composition is intended for treating virus-infected CD4+ lymphocytes, and (iii) sialyl-Lewis<sup>x</sup>, where the composition is intended for treating a region of inflammation.

22. The method of claim 15, wherein the liposomes further include a shielded ligand attached to the liposome effective to bind to a target cell surface receptor molecules after, but not before, chemical release of the hydrophilic polymer coating.

23. The method of claim 15, wherein said liposomes further contain a shielded cationic lipid effective to impart a positive liposome-surface charge, to enhance binding of liposomes to target cells after, but not before, chemical release of the hydrophilic polymer coating.

24. A method for screening a hydrophobic polymer for fusogenic activity with a target membrane, comprising adding to a suspension of target cells, a triblock copolymer composed of a segment of the hydrophobic polymer to be tested, and attached to each end of the polymer segment, through a chemically releasable bond, a hydrophilic polymer segment effective to solubilize the hydrophobic polymer segment in the suspension, releasing said hydrophilic polymers to expose said hydrophobic segments to said target cells; and analyzing said suspension for hemolysis of said target cells.

25. The method of claim 24, wherein said target cells are erythrocytes.

26. The method of claim 24, wherein said releasable linkage is a disulfide linkage, and said releasing includes adding a reducing agent to the suspension.

27. The method of claim 24, wherein said hydrophilic polymer is polyethylene glycol having a molecular weight between 1,000-5,000 daltons.

28. A polymer-lipid conjugate for use in promoting fusion between target membranes, comprising

a first segment composed of a hydrophilic polymer;  
a second segment composed of a hydrophobic polymer, said second segment joined to said first segment by a chemically releasable bond; and

attached to said second segment, a vesicle-forming lipid member.

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